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Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
8 July 1999 (08.07.99)

(54) Title: FUSION PROTEINS COMPRISING A DIMERIZATION, TRIMERIZATION OR TETRAMERIZATION DOMAIN AND AN ADDITIONAL HETEROLOGOUS TRANSCRIPTION ACTIVATION, TRANSCRIPTION REPRESSION, DNA BINDING OR LIGAND BINDING DOMAIN

(57) Abstract

The present invention relates to novel fusion proteins which activate transcription, to nucleic acid constructs encoding the proteins and their use in the genetic engineering of cells. Key fusion proteins of the invention contain at least two mutually heterologous domains, one of which being a bundling domain. Bundling domains include any domain that induces proteins that contain it to form multimers ("bundles") through protein–protein interactions with each other or with other proteins containing the bundling domain. Examples of bundling domains that can be used in the practice of this invention include domains such as the lac repressor tetramerization domain, the p53 tetramerization domain, a leucine zipper domain, and domains derived therefrom which retain observable bundling activity. Cells are engineered by the introduction of recombinant nucleic acids encoding the fusion proteins, and in some cases with additional nucleic acid constructs, to render them capable of ligand–dependent regulation of transcription of a target gene. Administration of the ligand to the cells then regulates (positively, or in some cases, negatively) target gene transcription.

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INTERNATIONAL SEARCH REPORT

I. ational Application No
PCT/US 98/17723

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/67 C07K14/39 C07K14/035 C07K14/47 C12N15/62
A61K38/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DANG C V ET AL: "INTRACELLULAR LEUCINE ZIPPER INTERACTIONS SUGGEST C-MYC HETERO-OLIGOMERIZATION." MOL CELL BIOL 11 (2). 1991. 954-962. CODEN: MCEBD4 ISSN: 0270-7306, XP002062827	1-4,6,8, 10,28,38
Y	see the whole document	5,7,9, 11-19, 29-74

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
6 May 1999	18.05.99

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hix, R

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/17723

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Y	see the whole document	5,7-12, 14-19, 29-74

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Ir tional Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
Y	LI, JUNYI ET AL: "Angiotensinogen gene activation by angiotensin II is mediated by the Rel (nuclear factor-kappa-B p65) transcription factor: One mechanis for the renin angiotensin system positive feedback loop in hepatocytes." MOLECULAR ENDOCRINOLOGY, (1996) VOL. 10, NO. 3, PP. 252-264. ISSN: 0888-8809., XP002101918 see page 259 - page 260 ---	20,21, 26-28
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INTERNATIONAL SEARCH REPORT

i. ational Application No
PCT/US 98/17723

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	RUBEN S M ET AL: "FUNCTIONAL CHARACTERIZATION OF THE NF-KAPPAB P65 TRANSCRIPTIONAL ACTIVATOR AND AN ALTERNATIVELY SPLICED DERIVATIVE." MOL CELL BIOL, (1992) 12 (2), 444-454. CODEN: MCEBD4. ISSN: 0270-7306., XP002101923 see the whole document ---	20,21, 26-28
Y	SCHMITZ M L ET AL: "THE P65 SUBUNIT IS RESPONSIBLE FOR THE STRONG TRANSCRIPTION ACTIVATING POTENTIAL OF NF-KAPPA-B." EMBO (EUR MOL BIOL ORGAN) J, (1991) 10 (12), 3805-3818. CODEN: EMJODG. ISSN: 0261-4189., XP002101924 see the whole document ---	20,21, 26-28
Y	WO 97 12040 A (SANDOZ LTD ;SANDOZ AG (DE); SANDOZ AG (AT); ANRATHER JOSEF (US); B) 3 April 1997 see the whole document ---	20,21, 26-28
P,Y	GUERMAH, MOHAMED ET AL: "Involvement of TFIID and USA components in transcriptional activation of the human immunodeficiency virus promoter by NF-kappaB and Sp1." MOLECULAR AND CELLULAR BIOLOGY, (JUNE, 1998) VOL. 18, NO. 6, PP. 3234-3244. ISSN: 0270-7306., XP002101926 see the whole document -----	20,21, 26-28

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INTERNATIONAL SEARCH REPORT

.rnational application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 53 to 56 and 63 to 67 encompass methods of treatment of the human/animal body carried out in vivo, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-19, 29-37, 39, 43-56,
58-74 and partially claims 28, 38, 40-42, 57

A recombinant nucleic acid encoding a fusion protein containing a "bundling domain" and at least one additional domain that is heterologous thereto, fusion proteins encoded therefrom, vectors, compositions and host cells comprising said nucleic acid and a method for identifying a moiety capable of binding to a protein or protein domain comprising using the said host cells.

2. Claims: 20-27 and partially claims 28, 38, 40-42, 57

A recombinant nucleic acid encoding a fusion protein containing at least one domain derived from a p65 transcription activation domain and at least one domain which is heterologous thereto, in which the p65-derived domain contains one or more of the mutations of figure 7, and fusion proteins encoded therefrom.

INTERNATIONAL SEARCH REPORT

Information on patent family members

tational Application No
PCT/US 98/17723

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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